SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES

ADVISORY PANEL

MEETING

December 7, 2006

Hilton Washington D.C. North
Gaithersburg, Maryland

Circulatory System Devices Advisory Panel Meeting

December 7, 2006

Attendees

Chairperson
William H. Maisel, M.D., M.P.H.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Voting Members
Sharon-Lise Normand, Ph.D.
Harvard School of Public Health
Boston, Massachusetts

Richard L. Page, M.D.
University of Washington School of Medicine
Seattle, Washington

John C. Somberg, M.D.
Rush University Medical Center
Lake Bluff, Illinois

Christopher J. White, M.D.
Ochsner Clinic
New Orleans, Louisiana

Clyde W. Yancy, M.D.
Baylor University Medical Center Dallas
Dallas, Texas

Consultants
Jeffrey A. Brinker, M.D.
The Johns Hopkins Hospital
Baltimore, Maryland

Michael J. Domanski, M.D.
National Institutes of Health
Bethesda, Maryland

L. Henry Edmunds, Jr., M.D.
The Hospital of University of Pennsylvania
Philadelphia, Pennsylvania

Robert Harrington, M.D.
Duke Clinical Research Institute
Durham, North Carolina

John W. Hirshfeld, M.D.
The Hospital of University of Pennsylvania
Philadelphia, Pennsylvania

Norman S. Kato, M.D.
Cardiac Care Medical Group
Encino, California

Warren K. Laskey, M.D.
University of New Mexico School of Medicine
Albuquerque, New Mexico

JoAnne Lindenfeld, M.D.
University of Colorado Health Science Center
Denver, Colorado

Douglas Morrison, M.D.
University of Arizona
Tucson, Arizona

Steve Nissen, M.D.
Cleveland Clinic Foundation
Cleveland, Ohio

Eric Topol, M.D.
Case Western Reserve Foundation
Cleveland, Ohio

George Vetrovec, M.D.
Medical College of Virginia, VCU
Richmond, Virginia

Judah Z. Weinberger, M.D.
Columbia University
New York, New York

Industry Respresentative
Pamela W. Adams
Senior Vice President, ETEX Corporation
Cambridge, Massachusetts

Consumer Representative
Linda A. Mottle, M.S.M., R,
GateWay Community College
Phoenix, Arizona

Executive Secretary
James P. Swink
Food and Drug Administration
Rockville, Maryland

FDA Participants
Geretta Wood
Director, Advisory Panel Program

Bram Zuckerman, M.D.
Director, Division of Cardiovascular Devices

Takahiro Uchida, M.D.
CDRH/ODE/DCD

Andrew Farb, M.D.
CDRH/ODE/DCD

Andrea Holton, Ph.D.
CDRH/OSB

Hesha Duggirala, Ph.D.
CDRH/OSB

Robert P. Fiorentino, M.D., M.P.H.
CDRH/DCD

Ashley Boam

CALL TO ORDER AND INTRODUCTORY REMARKS

Chairperson William H. Maisel, M.D, M.P.H., called the meeting to order at 8:04 a.m. He noted that the voting members present constitute a quorum and asked them to introduce themselves.

Geretta Wood, Director, Advisory Panel Program, read the conflict of interest statement. Full waivers have been granted to Robert Harrington, JoAnne Lindenfeld, Richard Page, George Vetrovec, and Clyde Yancy. She stated that Judah Weinberger no longer holds a financial interest requiring a waiver.

FDA PRESENTATION

Takahiro Uchida, M.D., Andrew Farb, M.D., Andrea Holton, Ph.D., and Hesha Duggirala, Ph.D., CDRH, presented a summary of FDA's perspective on drug-eluting stent (DES) thrombosis issues. Dr. Farb summarized the position of the agency. Available data indicate that DES implanted according to the labeled intended use are associated with reduced rates of repeat procedures for restenosis and with a small but significant increased risk of late stent thrombosis after one year compared to bare metal stents (BMS), but it has not been established that these events translate into increased rates of death and myocardial infarction (MI). There is only limited data on patients beyond three years. Studies indicate an association between premature discontinuation of antiplatelet therapy and increased rates of stent thrombosis, MI, and mortality, but the optimal duration, particularly in more complex patient and lesion subsets, has yet to be determined. Any recommendation for increased duration must balance any reduction in the incidence of stent thrombosis with a potential increase in the

risk of major bleeding. There is need for continued efforts to understand mechanisms of stent thrombosis and any interventions that reduce the risk.

Dr. Topol asked Dr. Farb to explain the disconnect between the excess of stent thrombosis and apparent lack of excess clinical events. Dr. Farb said one explanation is that the numbers of these rare events are too small to show a difference. These late events were unexpected and studies were not sufficiently powered to show any difference. Another possibility is that there are other confounders present.

Dr. Laskey asked if the events are occurring together in the same patient, and Dr. Farb said his impression is that there is not double-counting going on. Dr. Nissen asked if it was a relatively constant hazard or whether there was any evidence of attenuation over time. Dr. Farb said that is difficult to answer given the available data and the possibility of confounding factors. Dr. Nissen then asked whether there are any pill count based compliance measures. Dr. Farb said there was some useful data from the TAXUS ARRIVE 1data set.

Dr. Normand asked about effect size in terms of a clinically meaningful difference in stent thrombosis. Dr. Zuckerman said FDA is looking for input on that from the advisory panel. Dr. Normand noted that the data indicating a significant difference in mortality rates is from trials powered for the composite, not the individual measure. She also said it would be helpful to know the rate of stent thrombosis for BMS. Dr. Farb said the issue is when the stent thrombosis occurs.

Dr. Harrington asked how they had come up with the requirement for five-year follow-up in eighty percent of the patients and how the follow-up was actually done. Dr. Farb said follow-up in TAXUS after three years and in CYPHER after four is over 90

percent. Ashley Boam said eighty percent was the minimum based on expected loss to follow-up over five years. She thought the follow-up in most cases was done by telephone by the local site, and she said the blinding ended when the primary endpoint was reached.

Dr. Page asked if there was data on how many patients discontinued clopidogrel for cost or other reasons, and Dr. Farb said they had no such data. Dr. Lindenfeld asked about age in the clinical trials compared to the average age of real world patients. Dr. Farb responded that the inclusion/exclusion criteria may have skewed the distribution to a younger age group but didn't have specific data. Dr. Lindenfeld asked about factoring in non-compliance as the risk versus the drug part of that non-compliance. Dr. Farb said it is hard to tell whether there is discontinuation of both clopidogrel and aspirin or only of clopidogrel and that there have been events in patients who maintained dual antiplatelet therapy, so simply continuing clopidogrel will not solve the problem.

Correcting her previous remarks, Ms. Boam stated that the sites were still blinded during the ongoing follow-up in the clinical trials of both approved drug-eluting stents. Dr. Hirshfeld inquired whether they should focus more on the detailed analyses from the pivotal trials than on the real world experience which seems to have double the rate of adverse events. Dr. Farb agreed that it seems as if they should focus on the real world data and suggested the difference was linked to the inclusion/exclusion criteria of the clinical trials.

Dr. Domanski wondered if the disconnect between stent thrombosis and death or MI might be due to a therapeutic effect of the stents mitigated to a certain degree. Dr. Farb agreed that not having to return for another intervention is an important endpoint

and said that with the registry trials there is no control so there is no comparison to alternative therapies.

Dr. Edmunds asked whether any studies have demonstrated that the lining cells of the lumen are in fact fully functional endothelial cells. Dr. Farb said it has not been shown that they perform like endothelial cells in a normal artery but they have been proven to be endothelial cells through staining and scanning electron microscopy.

Dr. Morrison wondered if some of the apparent disconnect represents the difference between necessary and sufficient causation and said his impression is that with DES, even as opposed to BMS, there is an association between acute or subacute thrombosis and infarction. Dr. Farb said that prior to DES late stent thrombosis was seen in complex bifurcation lesions with very necrotic plaques and also late BMS thrombosis in highly restenotic plaques, but late stent thrombosis that presents with ST segment elevation is morphologically fundamentally different in that it shows absence of advanced healing.

Dr. Somberg asked if the agency is sure of the conclusion that there is a significant yet small incidence of late stent thrombosis. Dr. Farb said that based on what is known pathologically, data from the randomized trials, and important registries there is significant increase in late stent thrombosis after one year post-placement. Dr. Vetrovec asked if all the events being discussed are first events and noted that the disconnect may be reflected in the fact that patients with higher restenosis rates and BMS get more procedures, which lead to more events. Dr. Farb said it is censored when a patient has a restenosis event and hoped the sponsors would present data on outcomes following secondary procedures to treat restenosis.

Dr. White asked about the degree of off-label use of BMS which he believed is quite high. Dr. Farb said the point was well taken but did not have data. Dr. Normand asked whether anyone had looked at data on people who have multiple endpoints. Dr. Farb did not know and asked that the sponsors address the question.

Dr. Kato wondered if they were going down the road of making a mistake on a public policy recommendation in using very small numbers from studies not powered to detect such small differences. Dr. Farb acknowledged the limitations of the data and said the agency is interested in how the panel addresses the limitations in providing its advice.

FIRST OPEN PUBLIC HEARING

Herman Gold, M.D., Interventional Cardiologist, Massachusetts General Hospital, Boston, presented data from studies headed by Dr. Renu Virmani. He said the most powerful predictor of late stent thrombosis is the extent of endothelial coverage, and the best morphometric predictor is the ratio of uncovered to total stent struts per cross-section. Heterogeneity of healing within the DES is a frequent finding. The site of uncovered struts and thrombus formation most often localizes to the middle segment. The marked delay requires prolonged therapy. Angiographic late loss should not be the only discriminator. Arterial healing is an important endpoint, and potentially avoidable risk factors include malapposition, bifurcating lesions, and long lesions.

Alan D. Michelson, M.D., Director, Center for Platelet Function Studies, University of Massachusetts Medical Center, said the potential role of platelet function testing in late stent thrombosis may be to monitor non-compliance, resistance or hyperresponsiveness to aspirin and/or clopidogrel, and platelet hyperfunction after

discontinuation. Clinical studies are needed to determine whether testing can predict late stent thrombosis or other MACE.

Donald Cutlip, M.D., Beth Israel Deaconess Medical Center, recommended that stent thrombosis should be looked at within each of three time categories as well as overall, and he said that possible stent thrombosis adds significant noise to the overall rates and is unlikely to be the only signal of stent thrombosis. He concluded that the major safety outcome of DES relative to other devices or treatment strategies is best assessed by measures of overall mortality, cardiac mortality, or composites of mortality in myocardial infarction. Even if there is no measurable effect on mortality or MI outcomes, stent thrombosis is still a critical mechanism impacting safety. Definitions and analytical methods are critical, and small or immeasurable effects may be significant with more patients and more complex lesions.

Dr. Maisel asked Dr. Cutlip for his opinion whether there is a true very late stent thrombosis issue. Dr. Cutlip said there is a problem and highlighted the huge difference in overall rates when prior target lesion revascularization (TLR) is included and that many of these prior TLR events occur after restenosis treatment that included brachytherapy. He said the events that occur are very dramatic and that it is possible there are silent events which are not being picked up.

Dr. Somberg asked for data on the difference between target and non-target lesions and whether it is highly significant between BMS and DES. He also asked if there was a scientific basis for the breakdown of definite, possible, and probable. Dr. Cutlip said there is no right or wrong answer and that the goal is to establish consensus and hear from all stakeholders. In response to the first question, he said it was not

looking at target versus non-target lesion but simply the stented target lesion. He said it was all case by case and did not have summary data.

Dr. Normand asked Dr. Cutlip about not doing an intent to treat analysis and systematically excluding people and about group recommendations where different answers are possible. Dr. Cutlip recognized the problem with excluding patients but said clinically there is concern about doing pure intent to treat, particularly comparing BMS to DES. Dr. Norman asked if a new study design is needed. Dr. Cutlip said possibly and that it is problematic to relate a thrombosis event back to a BMS when brachytherapy, which is associated with a high risk of thrombosis, was used to treat restenosis occurring after BMS implantation. He agreed the endpoint is still important for the patient and in terms of strategy but said they do not know whether the outcomes of events associated with prior TLR are the same as primary events. He said it is important for observers to be able to see both analyses.

Dr. Nissen asked who funded ARC. Dr. Cutlip said for the Washington meeting each industry sponsor as well as HCRI contributed $1,000, but he was not involved in the finances for the other meeting held in Dublin. Dr. Nissen asked Dr. Gold about the relative roles of endothelialization and late malapposition. Dr. Gold said in all cases of thrombosis with DES there is delay in healing, and malapposition due to late arterial wall remodeling is important in the DES group but not with BMS.

Dr. Harrington asked Dr. Gold about clinical characteristics that may predict neoendothelializatioin and about the possible differential survival effect amongst patients with diabetes. Dr. Gold said the studies were too small to look at clinical indicators. One theoretical possibility is high resolution intravascular imaging to look at the percentage of

uncovered struts per stent segment. Lacking that, patients with complex bifurcating stenting and lesions that are very long seem to have higher incidence.

Dr. Harrington asked Dr. Michelson whether the platelet-rich white clots that form at the site of stent thrombosis are the same as are seen with acute MI. Dr. Michelson said platelet-dependent thrombi are important in both acute MI and stent thrombosis and said they are very similar in principle. Dr. Harrington inquired further about possible mechanisms of thrombosis other than non-compliance or non-response to clopidogrel or aspirin including inflammatory relationships between the stented segment and the blood, but Dr. Michelson did not know.

Dr. Somberg asked Dr. Michelson if it has been demonstrated that point of care monitoring of platelet variability responds to drugs or makes any difference in outcome. Dr. Michelson said some of the studies he cited used a point of care device including one by Chen et al. published in JAC.

Dr. Hirshfeld asked Dr. Gold about generalizing his autopsy observations to living patients. Noting that autopsy studies are limited, Dr. Gold said that in terms of the characteristics looked at clinically, the patients do reflect those seen in clinical practice and he noted that according to Dr. Virmani there is a significant difference in the autopsy results between the two types of stents.

Dr. Weinberger asked Dr. Gold whether the drug may be responsible for malapposition. Dr. Gold said in animal models they have done overlapping and specifically with CYPHER there is more necrosis of the arterial wall at overlap sites and that according to Dr. Virmani the space behind the stents is often filled with thrombus, which is unusual in malapposition but frequent with DES. Dr. Weinberger asked if there

is ever thrombus behind the stent that does not propagate into the lumen. Dr. Gold said it is likely a large problem if there is persistent thrombus in the setting of uncovered struts, and he noted that dual anti-platelet therapy was not completely protective in the autopsy series. Dr. Weinberger then asked if development of malapposition turns a healed stent into a functionally unhealed stent. Dr. Gold said yes and that he thinks it induces a state where late stent thrombosis is more likely.

DISCUSSION OF DES USE IN ACCORDANCE WITH THE LABELED INDICATIONS

Cordis Corporation

Campbell Rogers, M.D., Chief Technology Officer, described certain essential practices on which patients and physicians should insist. Data should be accurately analyzed and reported by people skilled to do so and with true equipoise. There should be common definitions to enable comparisons of studies. Patient-based clinical endpoints are essential in measures of device safety. Dr. Rogers noted that studies done by Cordis are not conclusive with regard to the appropriate regimen of anti-platelet therapy.

Dennis Donohoe, M.D., Worldwide Vice President, Clinical Research and Regulatory Affairs, reviewed safety data from pooled analyses of four randomized trials. With four-year follow-up and five-year extended follow-up for two of the trials, they found no significant difference in total mortality or cardiac and non-cardiac mortality nor for MI for the combination of deaths and non-fatal MI.

Laura Mauri, M.D., M.Sc., Chief Scientific Officer, Harvard Clinical Research Institute, reviewed the Academic Research Consortium (ARC) definitions and

focused on results of a blinded adjudication process. She said it is hard to come to strong conclusions on mechanisms with only a small number of events, but overall they found CYPHER patients and BMS patients had similar overall risk of stent thrombosis over four years and the curves remained convergent to the last available follow-up beyond four years. Though events occurred early, late, and very late in both arms, there were more before year one for BMS and more events after year one for CYPHER. The proportional hazards assumption was tested and not rejected. Patients with BMS were more likely to have stent thrombosis if they had TLR, and they had TLR more frequently. Though rare, patients with TLR following CYPHER stent did not have increased frequency of stent thrombosis. Clinical outcomes of stent thrombosis were similar for CYPHER and BMS.

Dr. Rogers concluded that CYPHER has demonstrated sustained benefit in reducing repeat revascularizations, and there is no significant difference in death and death or MI, but the temporal distribution of stent thrombosis may vary. He said that Cordis endorses the guideline that dual anti-platelet therapy be continued up to 12 months in patients with coronary disease and reasonably low risk of bleeding. More studies to determine optimal procedural techniques, more extended follow-up, and continued examination of the mechanisms of thrombosis are needed.

Boston Scientific Corporation

Donald S. Baim, M.D., Executive Vice President, Chief Medical and Scientific Officer, presented data from on-label use of the TAXUS drug-eluting stent. Randomized trials show marked reduction, across all studied subgroups, in repeat revascularization with a trend towards fewer deaths and less Q-wave MI. Rates of stent

thrombosis were not statistically significantly different from BMS for four-year cumulative or beyond one year rates using any definition. Data on Plavix use beyond six months showed a trend towards reduction in death and MI.

Dr. Nissen asked to see data on the excess of late malapposition. Dr. Mauri said they looked at a subset pre-specified for IVUS at eight months. In the CYPHER arm, 45 of 180 patients had incomplete stent apposition, and in the BMS arm 12 out of 145 did. Noting that Dr. Mauri's data is based on very small numbers, Dr. Nissen wondered about the actual percentage of patients that get late malapposition. Dr. Mauri said those numbers included patients with persistent and acquired incomplete stent apposition.

Dr. Nissen then asked about differential clopidogrel use and its possible effect on event rates if there is more clopidogrel use in the DES arm. Dr. Baim said there was double-blinding, and the percentage use of Plavix was nearly identical through four years. In the 12 month landmark analysis of BMS, there was very little effect of clopidogrel, but in the DES arm there seemed to be a benefit, though not sustained to four years. Dr. Baim noted that it was not significant. Dr. Donohoe said for the CYPHER trials clopidogrel use was only tracked for the first several months, and by six months most patients ceased antiplatelet therapy as per the protocol.

Dr. Somberg asked if either company had looked at the power to see small differences. Responding to an earlier question of Dr. Nissen, Dr. Baim said in 547 IVUS patients, late and complete acquired apposition was seen in 3.5 percent of control and 5.3 percent of TAXUS patients with a p-value of 0.37 and no stent thrombosis in either arm. Dr. Baim said the real world data he will present closely mirrors the TAXUS trials for similar patients. He said the trials were not powered to look at such differences, but there

are findings which are sufficient to say there is a low frequency of late thrombosis deserving of some remediation. He also said the concerns are based not on real world experience but on meta-analyses of parts of the trials that came to very different conclusions rather than looking at all the patients.

Dr. Rogers said their data does not rule out strut malapposition as a cause of thrombosis. He said the data they have is about strut malapposition at six months and the rates of thrombosis months or years later are no different. Dr. Somberg asked the companies to give the approximate power of their studies. Dr. Mauri said that according to FDA guidelines, the studies were designed to detect a one percent difference from a baseline rate of one percent, and she noted that the data has the strength of having a control group.

Dr. Normand asked Dr. Mauri whether she had estimates of sensitivity and specificity with regard to her indication that the definition selected balances sensitivity and specificity. Dr. Mauri said it had been a general statement and they do not have numbers. She said the issue is what is the gold standard, which in the past has been angiographic or pathologic confirmation. Dr. Normand asked whether a one percent difference in stent thrombosis is clinically meaningful, and Dr. Mauri said yes but that it needs to be determined what that represents in terms of overall long-term mortality. Dr. Normand asked what the one percent difference was in reference to, and Dr. Mauri said she believed it was stent thrombosis but that it might be better for FDA to answer that.

Dr. Normand asked Dr. Baim about the unit of analysis in the TAXUS trials and whether they had accounted for the fact that in two of the trials patients could have more than one stent. Dr. Baim said for death and MI the unit of analysis is the patient and for

stent thrombosis and repeat revascularization it is the stent. He also said there are trials with thrombolytic agents where a one percent difference in mortality was highly significant to the fate of a drug or therapy. He said the main impact of stent thrombosis is not as a primary endpoint but as one of several potential causes of death and MI.

Dr. Domanski said the key is focusing on the actual clinical event rate because it will be very difficult to know with precision the actual stent thrombosis rate in a real population. Dr. Topol asked both companies to comment on the fact that although both presentations concluded that there is no stent thrombosis statistical significance, neither had sufficient power to make that conclusion, and the trend is going in the wrong direction. He highlighted the analysis presented by Dr. Baim that offsets potential excess in stent thrombosis with no clinical event excess and wondered if Cordis had performed a similar analysis. Dr. Rogers said the effect on restenosis of the CYPHER stent is probably greater, but he said they would attempt to present data in a format similar to what was presented by Dr. Baim later in the meeting.

Dr. Topol asked whether there were MIs related to the repeat procedure as part of these events. Dr. Rogers said most of the post-TLR events in the CYPHER group did not seem to be peri-procedural infarctions. Dr. Baim said there were patients who presented with infarction as well as peri-procedural infarctions but the numbers were quite small.

Dr. Edmunds said they have shown non-inferiority to BMS and, in light of the disconnect between restenosis rates between the two kinds of stents, wondered how they could justify selling DES rather than BMS, which is roughly four times cheaper, to patients. Dr. Rogers noted that there is a real clinical burden of restenosis and thus real benefit to DES. Dr. Baim agreed and said he believes the data presented shows no

drawback of increased death or MI related to that substantial clinical benefit. Dr. Edmunds said there is still an unexplained disconnect.

Dr. Harrington asked about the power level to make a statement that the 1.3 percent difference in death favoring BMS is not statistically significant. He said that in the diabetic population there may be biological plausibility for why DES would perform worse and asked for the p-value for the interaction test. Dr. Mauri said it was underpowered to detect such a small mortality difference. Dr. Rogers said they have data out to five years showing between years four and five many patients in the BMS arm with diabetes died and very few in the CYPHER arm did, and the curves come back together and there is no significant difference at five years. Looking at other data from three other trials showed the same death rates for BMS and CYPHER for diabetic patients, and a multivariate analysis in BMS patients shows that diabetes predicts better outcomes.

Dr. Vetrovec asked for any data on adverse events and inflation pressures. Dr. Rogers was not aware of such data. He said the trials were blinded and imagined the pressures were the same. Dr. Baim said that he would show later that the same factors known for BMS as thrombotic risks also apply to DES, and under expansion of BMS was one of those factors. Dr. Baim said he believes the mechanism of early stent thrombosis is probably very similar.

SECOND OPEN PUBLIC HEARING

Gregg Stone, Columbia University Medical Center, provided his perspective on DES safety and efficacy. He said DES are a remarkable advance by preventing restenosis. Late stent thrombosis with DES is offset by the increased incidence of

secondary stent thrombosis events with BMS, and the highest quality data suggests no overall incidence of death and MI, so the current DES approval pathways are acceptable. Modifying trials to be powered for safety or long-term follow-up is unnecessary and would be overly burdensome. He also said that more rigorous post-market surveillance and an FDA Dear Doctor letter reinforcing the need to weigh risks and benefits for each individual patient would be appropriate. It is completely unknown whether long-term clopidogrel will reduce late stent thrombosis, and therefore the FDA regulated label mandate should not change.

Patrick W. Serruys, M.D., Ph.D., Erasmus Medical Center, Rotterdam, The Netherlands, presented data on behalf of Drs. Spaulding, Daemen, Boersma, and Cutlip. He emphasized that the subgroup analysis including diabetes was not prespecified and the number of fatal events in this subgroup was small making statistical assessment more difficult. Large-scale studies in patients with diabetes using death, MI, or stent thrombosis as the primary endpoint are needed. Long-term safety of the sirolimus-eluting stent in these patients should be reevaluated in comparison to BMS with a pooled analysis including the long-term result of the most recently completed randomized studies.

Dr. Laskey asked about censoring TLR because of its confounding effect. Mr. Stone said it confounds the mechanistic association between the initial stent and subsequent stent thrombosis. He said by not censoring you look at overall incidence of thrombotic episodes, each of which may or may not be related to the original stent, but the patient does not care what the cause is. Dr. Laskey then asked whether there is a statistically significant difference in stent thrombosis. Mr. Stone said while there is likely

an increased incidence of late stent thrombosis from both DES, there is not an overall difference in the thrombotic episodes.

Dr. Somberg asked if the three and six months of antiplatelet therapy is simply arbitrary. Mr. Stone admitted that they are relatively arbitrary and said the question is whether additional clopidogrel will eliminate stent thrombosis and be worth the risk and expense.

Dr. Normand asked Mr. Stone to explain the differences between what was presented in the meta-analysis using the group data versus the patient-level data. Mr. Stone said published data often has a denominator and percentage but no numerator, and many of the trials used are not even published yet, so incomplete data from abstracts and internet sources was used. Dr. Normand asked if his presentation and the meta-analysis used the same population, and Mr. Stone said for the most part. He said the difference has to do with the ability to have all of the data and that there was an extra year of follow-up data.

THIRD OPEN PUBLIC HEARING

Burt Cohen, Angioplasty.org, said that patients need more information to enable them to choose whether to get a DES and to comply with medications. DES are a wonderful advance but stents must be used in conjunction with Plavix. The public deserves responsive communication, participatory patient education, and ongoing patient support. Public education is a two-way street, and clinicians and regulators must listen to patients in order to minimize safety problems.

PANEL DISCUSSION

Dr. Maisel began by asking which definition of stent thrombosis should be used.

Dr. Somberg said there is no evidence and said all the definitions are arbitrary. Dr. Nissen was concerned about the fact that industry had funded the ARC definition process, and he said the most powerful analysis of the data is that defined by the protocol because it is prospective. Dr. Maisel said it was unreasonable to expect an independent group to be able to obtain and analyze patient level data from all the individual companies at no charge. He said the group had received only modest industry funding and that the research institutes which conducted the analysis are beyond reproach. Dr. Nissen said that for something of such great importance to public health transparency and process are very important.

Dr. Domanski said the problem is not knowing how much stent thrombosis there is and that clinical events should be the driver of the panel's recommendations. He did not really share Dr. Nissen's concerns about the ARC definitions and said that if they are used he would opt for the definite and probable. Dr. Harrington said that processes for developing definitions for clinical research or practice belong more properly in professional societies rather than independent investigators, but he applauded the ARC group and said the next step is to move to a more formal stage. Dr. Maisel agreed and noted there are likely conflicts of interest on those writing committees and panels as well.

Dr. Normand thought it premature to judge the ARC process without knowing exactly what it was and agreed with Dr. Maisel that many people have conflicts in this area. She said there seemed to be general agreement among those involved with the clinical trials on the definite or probable definition. Dr. Topol added that it will be important to use the definition going forward to obtain much more information in future studies. Dr. Yancy suggested using the protocol definitions used when the data was

obtained for discussion of the on-label use.

Dr. Zuckerman said they are trying to better understand the existing data and that the protocol definitions were somewhat limited. FDA would like the panel to use the ARC definitions to complement the protocol ones to get a better sense of the data. Dr. Maisel asked if anyone had an issue with the ARC definitions for future research. Dr. Somberg thought that was reasonable given that all are arbitrary, but he did not think strong signals shown using the previous definitions should be ignored. Dr. Domanski was concerned about committing future investigators to well though out but arbitrary definitions. Dr. Normand said arguments against retrospectively redefining an endpoint do not make sense given that the panel is engaged in retrospective analysis.

Dr. Nissen compared it to changing the rules of an ongoing game and worried about the result from using definitions never tested prospectively. Dr. Normand said they were trying to cut the data in a scientifically sound way. She repeated that the retrospective nature of the definitions was no argument against using them. Dr. Laskey was concerned about introducing something with greater false positivity rate and the effect on posterior probability. He wondered if they could somehow look at who would be moved from one category to another to help validate.

Dr. Maisel said it was beyond the panel's scope to do that kind of analysis. He said the definitions are complementary and that the panel is split on which data sets are appropriate and will look at both. Dr. Maisel next moved to the issue of censoring TLR.

Dr. Topol said this is an important issue as is the censoring of those lost to follow-up. Returning to the definitions, Ms. Adams said it is hard for companies to use the same definitions for their protocols and said however good the ARC definitions are they at

least allow for comparisons to be made. She also pointed out that extensive clinical studies are currently underway using definitions which may or may not align with the ARC definitions. With regard to loss of follow-up, Ms. Adams said that eighty percent had been set by FDA so numbers in the range of 94-97 percent are very high. Dr. Topol said complete follow-up would be in excess of 99 percent. Dr. Normand said they if you're talking about patients there should not be any censoring, but once people are censored we must ensure they are balanced in terms of other observable characteristics.

Dr. Maisel turned to the issue of a clinically significant rate of stent thrombosis. Dr. Weinberger talked about lifetime integrated incremental risk and said he would be happy with .5 percent for that but not per year. Dr. Somberg said death, MI, and stent thrombosis are all important and the issue is whether there is a problem and whether it is growing over time.

FDA QUESTIONS TO THE PANEL

1. When used in accordance with their labeled indications, are DES associated with an increased rate of stent thrombosis, death, or myocardial infarction compared to bare metal stents?

Some panel members felt that death and MI are not elevated but remained unsure about stent thrombosis. Another panel member said there is a strong signal for stent thrombosis, and reducing its frequency may yield improvement in death or MI risk. One panel member said he was fairly confident of an increase in stent thrombosis particularly in patients not on long-term clopidogrel. Another panel member said he had seen no evidence that the problem goes away over time, so the obvious early advantages may well be overwhelmed by late hazard. Some panel members felt that the treatment is highly efficacious and has acceptable but serious potential hazards. Panel members generally agreed that there is not an associated increase in death or MI.

Dr. Maisel asked about the higher rate of deaths with the CYPHER stent. Panel members felt there is not enough data but thought it wise to watch out for a potential trend. Dr. Zuckerman pointed out that the difference in mortality for Cordis seemed to be driven not only by small numbers but by a single trial. Addressing diabetes, he said it had not been well defined in the studies nor had patients' adjunctive treatments been well classified. He mentioned an ongoing NIH diabetes DES trial but said enrollment was lagging.

One member said it appears that excess of death from the CYPHER experience seemed to be localized to patients with diabetes. Another emphasized the conflicting data on diabetes and said diabetics usually do poorer but did not think the signal was strong enough to include any warning in the labeling.

Dr. Maisel said the panel was generally unsure of the magnitude of any excess risk of stent thrombosis and how that risk will change over time and felt that further studies are needed to accumulate more patients at later time points. He said they are concerned about a potential signal but see no conclusive evidence of any increase in death or MI associated with DES. Some panel members were concerned they had not been given the data supporting Dr. Stone's summary of individualized data.

If a DES safety concern exists:

a. What is the relationship, if any, between stent thrombosis and clinical endpoints such as myocardial infarction or cardiac death?

Dr. Maisel said there does not seem to be a connection. One panel member said another possibility is that the studies are simply not highly powered enough. Dr. Zuckerman mentioned Dr. Baim's slide which helped to show two distinct entities and wondered if Cordis had such data. One panel member said the question was unclear. Ms.

Boam said one aspect is whether the numerical excess signal of stent thrombosis translates into clinical endpoints, and the other is in regards to death and MI as surrogates for probable or possible stent thrombosis.

Dr. Maisel said there is clear association between someone having stent thrombosis and death or MI but that they do not have data whether there is any difference between DES and BMS.

b. Compared to BMS, are DES associated with an increased rate of all-cause mortality?

Dr. Maisel said they had already discussed this and that there is no conclusive evidence of an increased rate of all-cause mortality with DES.

c. Do the safety concerns apply equally to both of the currently approved DES?

Dr. Maisel said there had been no evidence presented showing that the safety concerns do not apply equally. One panel member said certain trends indicate the two stents do behave differently but noted it is still based on small numbers. Dr. Maisel said the safety concerns apply equally but may not be the same.

d. Do the safety concerns outweigh the benefits for DES compared to BMS (i.e., reduction in repeat revascularization procedures)?

There was general agreement that there is nothing to suggest that DES safety concerns outweigh its benefits. Some panel members talked about real world concerns such as inability of many patients to afford Plavix and the differences between trial subjects and real-world patients and said they do not know whether the concerns will outweigh the benefits once the data is available.

e. Should the current labeling (indications, contraindications, warnings or precautions) be modified? If so, please provide your recommendations for modifications.

Dr. Maisel recommended including analyses using both the protocol defined endpoints and the ARC endpoints and perhaps the meta-analysis as well. Some panel

members agreed with the idea of full disclosure of what is currently known. One panel member said the label should only include a distillation of the data and say something about the possible signal regarding the risk of stent thrombosis. Dr. Maisel was hesitant to say anything about the risk of stent thrombosis other than that antiplatelet therapy may reduce it.

Dr. Zuckerman said the labeling could include different analyses using different definitions but that there should be a single interpretation that has undergone regulatory review. He also said information should be shared with patients and highlighted the critical importance of the pharmaceutical part of the therapy. Dr. Zuckerman suggested including point estimates in the clinical trial section of the label but noting that the associated confidence intervals are wide. Panel members agreed. One panel member emphasized that the label should indicate which patients the data applies to.

Dr. Zuckerman asked if the additional data needed would best be obtained through real-world registries rather than randomized trials. One panel member did not think it possible to get a large enough registry sample that does not include off-label use of the devices.

2. Current data indicate that termination of dual antiplatelet therapy prior to the duration as recommended in the DES label is associated with a higher risk of stent thrombosis. Current ACC/AHA/SCAI PCI Practice Guidelines recommend clopidogrel therapy for at least 3 months after CYPHER stent implantation, at least 6 months after TAXUS stent implantation (reflecting the recommendations in the present label for the CYPHER and TAXUS stents, respectively), and ideally up to 12 months in patients who are not at high risk of bleeding (Class IB recommendation). The European Society of Cardiology recommends clopidogrel administration for 6 to 12 months after DES implantation (Class IC recommendation).

Given the currently available data please consider the following questions:

a. Do the current data support a recommendation for an extended duration of dual antiplatelet therapy?

i. If extended dual antiplatelet therapy is recommended, what duration of administration would you recommend, and what data support this recommendation?

Panel members noted that most patients complied with the three or six months required and what happened after that was not randomized. Some panel members were reluctant to change the recommendation without compelling evidence that there would be any benefit.

One panel member disagreed since the patients studied generally did not follow the label indications and was compelled by the landmark analysis showing benefit at least through twelve months, but he referred to an earlier comment regarding the fact that patients in the randomized trials are at fairly low risk of bleeding. One member suggested the label could include a statement that in observational studies it appears that outcomes are better with continued duration but the impact on the overall event rate remains unknown because of bleeding.

One panel member said the data presented seemed to suggest that patients may be as likely to develop stent thrombosis on antiplatelet therapy as off, but another disagreed. As one of the authors of the paper, Dr. Harrington said there are multiple pieces of evidence but stated that he finds BASKET-LATE compelling in that it seems there is an accumulation of risk in DES patients off clopidogrel. He said that he recommends indefinite clopidogrel with the caveat that bleeding issues must be discussed. Another member wondered why the recommendations for the on-label patients should be changed based on studies of more complex, off-label patients.

Dr. Maisel said he would be hesitant to make a recommendation since there seems to be no analysis measuring bleeding risk in addition to reduction in stent thrombosis. A

panel member said they need an observational study which attempts to randomize who stops and continues.

Dr. Maisel suggested that they have seen no data that suggests they should either change the label or overturn national guidelines already in place. One panel member thought it reasonable for the label to mention the AHA ACC general recommendation of one year of Plavix after stent placement in appropriate lower risk individuals. Another suggested the label should include the recommendations from each device's randomized trials but also say that dual antiplatelet therapy duration must be related to a patient's overall risk.

Comparing Dr. Harrington's paper to data presented by Dr. Baim, one panel member said the difference is that Dr. Harrington's work found no major difference in BMS with and without clopidogrel, and she talked about estimates of bleeding with antiplatelet agents from the literature. Dr. Maisel said some randomized trials have shown a two percent bleeding risk with Plavix. Another panel member wondered if mortality goes up with the frequency of bleeding.

One panel member felt the label should include a statement of what percent of patients in the randomized trials continued past the recommended duration. Another agreed but did not think observational data should be in the label because it is not necessarily from the same population as the clinical trial cohorts. Another disagreed and thought the data compelling enough to be included.

Dr. Zuckerman stated that observational data is frequently included in device labels and thought it would be fine if well constructed. Dr. Maisel said that the current

AHA ACC guideline would be included as well as a statement of to what extent patients in the particular trials continued on Plavix past the duration recommended in those trials.

ii. If an extended dual antiplatelet therapy is recommended, would you further recommend restarting dual antiplatelet therapy in stable patients who have already stopped clopidogrel?

Dr. Maisel said no for patients greater than twelve months out. Panel members generally did not think there should be any recommendation given the lack of data on reintroducing antiplatelet therapy. One panel member said the statement should simply be to discuss it with the physician, and Dr. Maisel agreed.

b. If anti-platelet therapy needs to be stopped due to a concurrent compelling medical condition, what strategies do you recommend to reduce the risk of DES thrombosis until antiplatelet therapy can be reinstituted?

i. If the patient were to remain on only one of the two antiplatelet agents (aspirin or clopidogrel), which agent should be continued?

One member noted that antiplatelet therapy should only be stopped for appropriate reasons after consideration by the patient and the cardiologist rather than some other type of physician. Other members disagreed. The panel discussed the importance of educating health care providers regarding the importance of antiplatelet therapy with DES.

One panel member suggested limiting it to six months but acknowledged the continuing difficulty of the lack of data. Another suggested saying simply that risk is a function of time since the procedure, but Dr. Maisel noted they do not even really know that. Another advocated simply including randomized trial data and letting physicians draw their own conclusions. One member wondered if there were any data on the temporal relationship between discontinuation and in-stent thrombosis.

One member pointed out the potential difference between stopping randomly and stopping for a surgery during which platelets will be turned on. The industry representative noted that much of what is being discussed is already part of the labeling. Dr. Maisel suggested saying that patients should not stop without consulting their

physician and the patient and physician should decide based on the patient's risk benefit profile before stopping prematurely. Another suggested simply saying that if a patient has to stop for any reason then it should only be done with the advice of the patient's physician. The industry representative noted that the labeling already says that.

DISCUSSION OF BROADER USE OF DES AND ITS IMPLICATIONS

Robert P. Fiorentino, M.D., M.P.H., CDRH/DCD, gave the FDA presentation on off-label use of DES. Challenges include frequent overlap between subsets and their definitions, variable or evolving clinical practice, lack of adequate control arms, possible lack of accepted standards of care, limited data on BMS in complex lesions, lack of data on adherence to antiplatelet regimens, studies underpowered for patient and lesion-specific subset analyses, meta-analyses may not capture patient-level data, the need to standardize the definition of stent thrombosis, variable length of follow-up, and limited long-term data. He concluded that the data comes from a variety of studies, each with its own strengths and weaknesses and each contributing part of the big picture of the risks of stent thrombosis in the broader population.

Dr. Baim discussed real world use of the TAXUS stent. His conclusions were that TAXUS in complex lesions has slightly higher event rates that compare well to real world complex PCI and CABG. Lacking results from randomized studies of even more complex patients, there is data showing that current clinical use exposes patients to excess risk when compared to available alternative revascularization therapies.

Sidney A. Cohen, M.D., Ph.D., Group Director, Clinical Research, Cordis Corporation, discussed off-label use of the CYPHER stent using data from randomized trials as well as Cordis-sponsored registries. He said that it is serving a significant unmet

clinical need and has better outcomes than either CABG or BMS. The benefit is similar to what was seen in the RAVEL and SIRIUS trials, but the risk is higher. However, randomized clinical data indicates that that elevated risk is also present in BMS, which indicates that it is most likely due to the fact that the patient and lesion subsets are at higher risk. Data is insufficient to support patient or lesion-specific labeling for dual antiplatelet therapy.

Dr. Maisel asked Dr. Baim to comment on the apparent trend towards higher and higher risk as you move further away from clinical trial patients. Dr. Baim said they are small numbers of events and not statistically significant. He said the events are higher in the first year, mostly the first thirty days, and that there was no signal of a significant difference after one year.

Dr. Somberg asked Dr. Cohen why he only presented one year of follow-up. Dr. Cohen said they had not known that very late stent thrombosis was an issue until most of the registries had already begun or been completed and that the J-CYPHER registry will have five years follow-up. Dr. Somberg also asked for data on stopping dual antiplatelet therapy early. Dr. Cohen provided data from the OUS e-CYPHER registry that at 30 days there was 85.6 percent, at 180 days 70.3 percent, and at 360 days 43 percent on dual antiplatelet therapy. Dr. Somberg then asked for data on the difference in terms of late stent thrombosis between those who maintained dual antiplatelet therapy and those who did not at those time points. Dr. Cohen said he did not have that data because most of their efforts went towards readjudicating registry data using the ARC definition since the data was not managed in-house. Dr. Somberg hoped the data would be provided to FDA when available.

Dr. Normand asked Dr. Baim why he used historical CABG as the comparator and why there is no concurrent data. Dr. Baim said that the patients would not have been treated with BMS so CABG was a more appropriate comparison and that in the SYNTAX trial the standard of care for left main and three vessel disease is surgery. He said that they did not have access to contemporary surgical data.

Dr. Topol asked about the one-year cut-off related to the fact that late stent thrombosis manifests after one year and about the completeness of follow-up. Dr. Cohen said OUS e-CYPHER had 88 percent, U.S. e-CYPHER 98 percent, DISCOVER 89.6, and STLLR 93.6 percent. Dr. Baim said that ARRIVE 1 and 2 have 80 to 90 percent follow-up at the protocol milestones. Dr. Topol also asked Dr. Baim about the use of historical data. Dr. Baim wondered what better control group there was short of doing a randomized trial.

Dr. Kato was also concerned and did not understand the methodology and said the current mortality rates for CABG are nowhere close to 6.5 percent. He asked if they matched risk factors and randomized various factors, and Dr. Bam said they did not have access to primary data for these published series. He said SYNTAX will randomize 2000 patients to contemporary CABG and follow-up data will be available in one year.

FOURTH OPEN PUBLIC HEARING

Antonio Columbo, M.D., EMO Centro Cuore Columbus and San Raffaele Scientific Institute, Milan, Italy, said the overall incidence in the series described was 1.9 percent and that no patients with acute MI were included. Half of patients had stent thrombosis within the first thirty days, and discontinuation of dual antiplatelet therapy was the most powerful predictor of stent thrombosis during the first six months.

Discontinuation of thienopyridine after six months does not appear to increase risk of stent thrombosis.

Lars Wallentin, Uppsala University, Sweden, discussed an independent Swedish registry with complete 100 percent follow-up. He described the registry and said there were differences going in both directions between the BMS and DES patients.

Bo Lagerquist, Uppsala University, Sweden, presented results from the Swedish registry. He concluded that after adjusting for differences, there was no significant difference in the composite of death and MI. But after six months the DES group showed a twenty percent relative increase in death and MI corresponding to an early absolute increased risk of .5 to one percent and 32 percent relative increase in mortality corresponding to a yearly absolute increased risk of about .05 percent. These increased risks remained unchanged through the end of the follow-up period. The restenosis rate was cut in half but corresponds to absolute reduction of only around three percent. Alternative or contributing explanations for these differences include non-registered differences between the groups as well as differences in the need for long-term protection by dual antiplatelet therapy.

Dr. Serruys presented clinical practice data from a large non-randomized two institution core study based on Bern and Rotterdam. Angiographic stent thrombosis with DES occurred with an incidence density of 1.3 in 100 patient years and a cumulative incidence of 2.9 percent at three years. The incidence continued at a steady rate of .6 percent per year for the first three years. There was early and late stent thrombosis with both drug-eluting stents with no significant difference between them. Local practice determined stent type and antiplatelet therapy, and analysis was limited to angiographic

stent thrombosis. IVUS was not routinely performed, and there was no direct comparison with the BMS population.

Takeshi Kimura, M.D., Kyoto University Hospital, presented preliminary one year data from the J-CYPHER registry. Stent thrombosis up to one year with corrected ticlopidine regimen seems lower in comparison to other real world registries in spite of the rather high prevalence of high risk patients. Although there is data only out to one year, attenuation of the rate was seen between six months and one year. A two-stent approach for bifurcation and hemodialysis was identified as an independent predictor for stent thrombosis. Other more common factors such as diabetes, CKD not on HD, and multivessel stenting did not have an adverse effect on stent thrombosis. Extended dual therapy up to one year did not have a favorable effect compared to discontinuation of thienopyridine within one year. Compared to a historical control of BMS, PCI using sirolimus-eluting stent (SES) was associated with similar mortality, less MI, and strikingly less TLR at one year despite the prevalence of more morbid patients.

Adnan Kastrati, M.D., presented results of meta-analyses of randomized trials of SES verses paclitaxel-eluting (PES) or bare metal stents. He concluded that the analysis shows no difference in long-term mortality and MI between SES and BMS or SES and PES. However, SES maintains superiority in overall reduction of MACE long term. Diabetes remains the best prognostic factor following use of both DES, but the likely negative impact of diabetes in the BMS arm of the SIRIUS trial must be clarified. There was no significant interaction between presence of diabetes and type of stent used with regard to mortality and MI.

Gerrit-Anne van Es, Ph.D., Director of Research and Development, Cardialysis, The Netherlands, presented the adjudication of events from the ARTS II trial. Patients with two or three vessel disease, events up to three years were adjudicated using the ARC definitions. For definite/probable, the following were observed: 1.2 percent subacute stent thrombosis, zero to thirty days; 1 percent late stent thrombosis, thirty days to one year; and 2.3 percent very late stent thrombosis, one to three years. Complete three year follow-up and event adjudication will be presented at ACC 2007. Potential risk factors observed in post hoc analysis include insulin dependent diabetes, renal function, and bifurcation stenting. The findings can only be verified by prospective randomized control clinical trials.

Dr. Nissen asked if the large and sudden drop-off in use of DES in the Swedish registry was due to preliminary results becoming publicly available, and Dr. Wallentin said yes. Dr. Nissen asked if they had concluded the late hazard overcame the early advantage by two years out, and Dr. Wallentin said that journalists had made that conclusion and that there was over interpretation of the results.

Dr. Harrington asked about standard antiplatelet use in Sweden and whether they had access to pharmacy records. Dr. Lagerquist said no but they will be able to in the future. He guessed that most patients had dual antiplatelet therapy for six months. Dr. Wallentin said most hospitals recommended three to six months and one twelve months. He said medicines over a certain amount are free in Sweden so there should not have been any economic reasons for people not to comply.

ADJOURNMENT

Dr. Maisel adjourned the meeting at 6:27 p.m. to reconvene the following day, Friday, December 8, 2006, at 8:00 a.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel on December 7, 2006, and that these minutes accurately reflect what transpired.

James P. Swink
Executive Secretary

I approve the minutes of the December 7, 2006, meeting as recorded in this summary.

William H. Maisel, M.D., M.P.H.
Chairperson

Summary prepared by
Eric C. Mollen
Neal R. Gross & Company
1323 Rhode Island Ave., N.W.
Washington, D.C. 20005
(202) 234-4433
eric.mollen@gmail.com